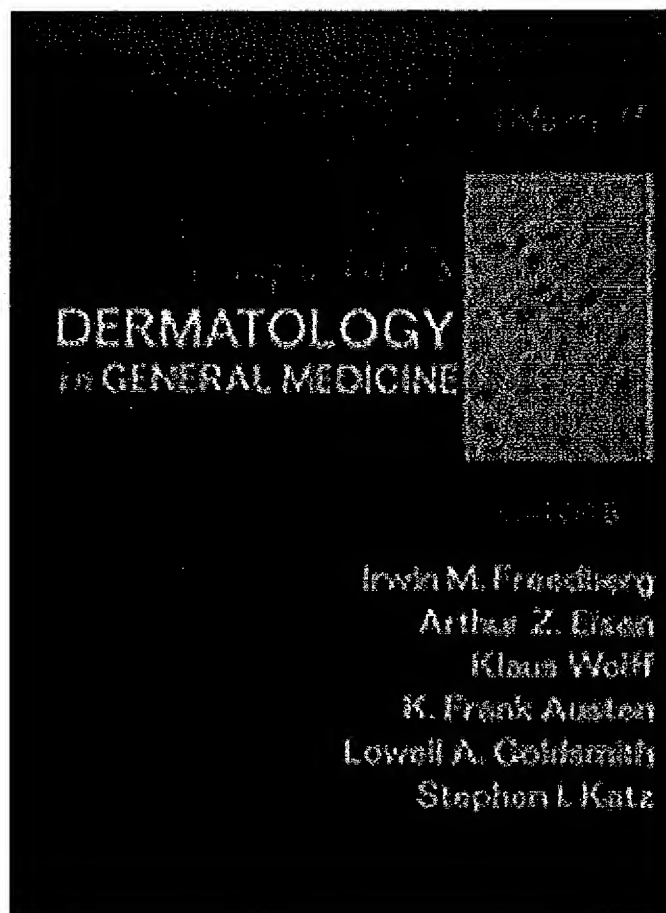


Exhibit B



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CHAPTER 267

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R. Rox Anderson

Lasers in Dermatology

Lasers in medicine defy simple characterization. New technology and new surgical and diagnostic applications for lasers are steadily being conceived. Lasers serve goals as diverse as revascularization of ischemic cardiac tissue, precise sculpting of the cornea, pulverizing urinary stones, and imaging cancers in vivo. Dermatology has been deeply affected by lasers, using them as precise and tissue-selective surgical tools.

ELECTROMAGNETIC RADIATION AND THE LASER BEAM

For centuries, physicists debated the nature of light. While Maxwell and his English colleagues argued that visible light behaved as particles, Fresnel and the French physicists maintained that light behaved as a wave, accounting for phenomena such as diffraction, constructive and destructive interference. Both views are correct, a "duality" now pervasive in quantum physics. Proof that electromagnetic radiation (EMR) travels as discrete particles, or *quanta*, of energy came when Einstein demonstrated that light can liberate single electrons off of a metal foil plate. This led to the present view that all matter and energy—everything in the universe—is quantized. EMR is now conceptualized as a fundamental form of energy, propagating through space at a constant speed c , as a wave but comprised of discrete quanta known as photons. As expressed by Planck's law ($E = h\nu = hc/\lambda$, where E = energy, ν = frequency, λ = wavelength, c = speed of light, and h = Planck's constant), photon energy is proportional to wave frequency and inversely related to wavelength. Consequently, shorter wavelength photons carry more energy. The EMR spectrum ranges from

long-wavelength, low-energy radio waves and microwaves to short-wavelength, high energy x-rays.

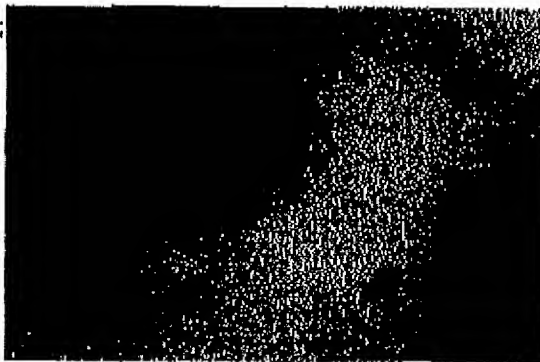
When EMR encounters skin, photons are absorbed by individual molecules, called *chromophores*, and/or scattered by structures in the skin. Scattering is a change in the direction of propagation of light, and accounts for reflection from skin. Absorption extinguishes a photon, and all of the photon energy is transferred to the chromophore molecule that absorbed the photon. Without energy absorption, no photon-tissue interaction can occur. Ionizing forms of EMR such as x-rays and short-wave ultraviolet (UV) light impart enough energy to strip electrons from the absorbing molecules entirely. In contrast, optical radiation has the right quantum energy for moving electrons between their molecular orbit levels. This is the basis for photochemistry, in which a photon provides the activation energy for chemical reactions. For example, visible light is visible because its photon energy exactly matches the activation energy for rhodopsin to isomerize, initiating a retinal action potential. Optical wavelengths are generally expressed in nanometers ($1 \text{ nm} = 10^{-9} \text{ m}$). Infrared radiation, which has a longer wavelength and lower photon energy than visible light, generally excites vibrational and rotational motions, generating kinetic energy (heat).

LASER is an acronym for light amplified by stimulated emission of radiation—a process that explains how the unique characteristics of laser light are obtained, illustrated in Fig. 267-1(A). The creation of light is conceptually the inverse of absorption—a photon is created when an electron jumps to a lower-energy orbital. In most light sources, this is a spontaneous, random process. In contrast, laser photons are stimulated into existence by each other. Electrons in the laser medium are first excited to a metastable state, which will eventually return to the preferred ground state by emitting energy. In stimulated emission, a photon triggers the release of metastable state energy in the form of a second, identical photon. Thus, amplification of light is achieved. The

FIGURE 267-5



A.



B.

Epidermal nevus in the neck before (A) and after (B) treatment with a rapidly scanned CO₂ laser.

Melanoma should be responsive to Q-switched lasers capable of selectively targeting melanin, yet this has not been the case in practice. Rather, all forms of melanoma have proven refractory to laser treatment, with recurrence or even pigment darkening being the rule. There is little doubt that Q-switched laser treatment destroys the dermal melanophages present in the dermal form of melanoma, but treatment necessarily damages the epidermis in the process, potentially further melanoma. Patients with refractory facial melanoma or postinflammatory hyperpigmentation typically do not improve after Q-switched ruby laser treatment.⁴⁴ Transient improvement had been noted after using erbium:YAG skin resurfacing to treat refractory facial melanoma; however, all patients experienced significant postinflammatory hyperpigmentation.⁴⁵ At present, laser treatment of melanoma cannot be advocated as a single-line therapy, although judicious use of Q-switched laser irradiation or erbium:YAG resurfacing in combination with topical bleaching creams and sun protection may yield cosmetic improvement in some individuals.

Laser treatment of postinflammatory hyperpigmentation is less disappointing, but variable, especially in darker skin types prone to laser-induced pigment alteration. In lighter skin types, however, Q-switched lasers such as the ruby, alexandrite, and Nd:YAG have been used to treat postinflammatory, or drug-induced, hyperpigmentation with good

results. In contrast to postinflammatory hyperpigmentation, which is caused by melanin pigment incontinence, postinflammatory hyperpigmentation is caused by vessel rupture, erythrocyte extravasation, and perivascular hemosiderin deposition. Hafszoll et al. used the Q-switched ruby laser (5.6 to 10.5 J/cm²; 4-mm spot size) to treat this common sclerotherapy complication in eight patients, noting significant lightening in 92 percent of treated areas.⁴⁶

Drug-induced hyperpigmentation may be caused by dermal and epidermal deposition of drug metabolites, hemosiderin, melanin, or a combination of pigment types. The unwanted pigmentation—which can vary from slate-gray to blue, lilac, brown, yellow, or red depending on the culprit drug—often follows a photodistribution (e.g., amiodarone, imipramine), but may also occur on mucosal surfaces, nails, teeth, or in a generalized distribution (e.g., minocycline, busulfan). Q-switched ruby, alexandrite, and 1064 nm-Nd:YAG lasers have all been used to lighten minocycline-induced cutaneous hyperpigmentation with good results. Significant cosmetic improvement has also been reported by using Q-switched lasers to treat amiodarone- and imipramine-induced hyperpigmentation.

Exogenous Dermal Pigment: Tattoos

Prior to the advent of Q-switched laser technology, individuals desiring tattoo removal had to choose between keeping their tattoo or accepting a scar in its place. While a major step forward, Q-switched laser treatment of tattoos is still far from ideal. In skilled hands, ablative techniques, including excisional, dermabrasion, cryotherapy, excision, and CO₂ laser vaporization, are capable of yielding cosmetically acceptable results, yet none can promise uniform, scar-free tattoo removal. With the introduction⁴⁷ and subsequent refinement of Q-switched laser technology for the treatment of tattoos, selective removal of tattoo pigment without scarring became a real clinical possibility.

An ideal treatment should remove all traces of tattoo pigment without leaving residual scarring. Most tattoo pigment particles are localized to lysosomes, primarily within dermal fibroblasts, macrophages, and occasional mast cells.⁴⁸ Pigment particles also range from about 2 to 400 nm, with the predominant pigment type being an oval-shaped 40-nm granule. Q-switched lasers produce nanosecond pulses, thereby achieving thermal confinement within individual lysosomes. With Q-switched laser treatment, the irradiated pigment particles reach peak temperatures in excess of 3400°C (3722°F) within nanoseconds, producing internal changes such as mechanical rupture and chemical alteration (e.g., combustion for carbon-based particles). Taylor et al. and others have described the morphologic appearance of such irradiated pigment particles as "lamellated" or "shell-like," with central zones of lucency and diminished opacity.⁴⁹ These intrinsic structural and chemical changes alone may account for some of the tattoo lightening that follows Q-switched laser irradiation. Each heated pigment particle also vaporizes a shell of water surrounding it, creating a shock wave that may contribute to the mechanical rupture and dispersion of the pigment throughout the host cell. Cell rupture and release of pigment fragments into the extracellular space occurs, and the ink is partially eliminated via lymphatic drainage, phagocytosis, or trans-epidermal elimination—all proposed mechanisms of posttreatment tattoo clearance. Strategies to augment these "pigment-elimination pathways" may hasten the process of tattoo lightening. In addition, there is some evidence that a new generation of picosecond-pulsed lasers may be even more effective at achieving both dermal and internal confinement within individual tattoo pigment particles, leading to enhanced photomechanical effects and more effective tattoo pigment clearance.⁴⁹ At present, technological and cost constraints have limited the clinical availability of picosecond lasers.

Over the past decade, the term "laser tattoo removal" has found its way into popular culture, and there is a current misconception that modern lasers can simply erase any tattoo. Recently, the Institute of